REMARKS

Claims 1-5 and 8-18 are pending in the application. Claims 1-5 and 8-18 are rejected. Upon entry of this amendment, which is respectfully requested, Claim 1 will be amended.

Claim 1 has been amended to recite methods of combating sub-dermal inflammation in the soft tissues which involve administration of a strontium compound.

Support for the amendment to Claim 1 may be found at least at page 2, line 30.

No new matter is added.

Response to Claim Rejections - 35 U.S.C. § 103

Claims 1-5, 8-18 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hahn et al. (US Patent No. 5,804, 203, "Hahn") in view of De Lacharriere et al. (US Patent No 5,866,168, "De Lacharriere"), Denhem et al. (Radiotherapy & Oncology, 2002, 63, 129-145, "Denhem") and Remington's Pharmaceutical Sciences (17th ed. 1985 page 1121-1122, "Remington's").

At page 2 of the Office Action, the Examiner states that Hahn discloses the use of strontium for treating the causes of inflammation and that a skin penetration enhancing agent can be used to reduce the amount of strontium. The Examiner admits that Hahn does not expressly teach the treatment of inflammation *per se* with strontium, the use of dimethylsulphoxide (DMSO) as a permeation enhancer or the treatment of inflammation associated with radiation therapy or arthritis. In order to compensate for these deficiencies, the Examiner cites De Lacharriere, Denhem and Remington's. According to the Examiner, De Lacharriere discloses that strontium is effective in treating inflammatory diseases such a rheumatoid arthritis and Denhem teaches that radiation therapy can cause inflammation of the skin tissues. Remington's is cited as teaching that DMSO is an anti-inflammatory and permeation enhancer.

The Examiner asserts that one of ordinary skill in the art, would readily use strontium to treat inflammation *per se*, and expect it to effective, because strontium is effective to treat the causes of inflammation. Additionally, the Examiner states that the skilled artisan would have readily recognized that DMSO would increase the bioavailability and anti-inflammatory activity of the strontium. Accordingly, the Examiner concludes that the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

In response, although Applicant disagrees with the Examiner on this rejection, solely to advance prosecution of the present application, Claim 1 has been amended to recite that strontium is administered "to combat inflammation arising from a condition associated with or without pain wherein the inflammation is sub-dermal and in soft tissue"

A distinction exists between treatment of the underlying causes or triggers of a disease or condition which happens to be associated with inflammation, and treatment of the inflammatory process *per se*. The present invention is concerned with the latter of these. Specifically, Applicant has surprisingly found that strontium compounds are particularly effective in combating inflammation *per se* which occurs in the soft tissues at the sub-dermal level. Importantly, none of the references cited by the Examiner discloses the use of strontium in methods of combating sub-dermal, soft tissue inflammation. Furthermore, none of the references, either alone or in combination, provides the required motivation to use strontium in such methods. Accordingly, Applicant submits that this rejection is not sustainable in view of the presently amended claims.

Additionally, Applicant submits that the present invention as a whole is not obvious over the prior art for the following reasons.

Hahn is directed to formulations that comprise an anti-irritant amount of strontium and their use in methods for reducing skin irritation. The reference is primarily concerned with reducing or preventing the irritation caused by topically applied products, in particular cosmetics and other skin care products. Hahn also mentions the use of strontium in reducing or preventing intrinsic irritation associated with various skin diseases, such as eczema, or caused by environmental conditions (e.g. sun, wind, etc.). The Examiner notes the reference at col. 9, lines 13-25 to suppressing skin irritation "due to tissue inflammation". However, as acknowledged by the Examiner, the reference does not teach the use of strontium in treating inflammation *per se*. Moreover, it is quite clear that the reference is concerned only with the treatment of irritation on the skin's surface. Thus, there is no teaching in Hahn with respect to the use of strontium in treating sub-dermal inflammation.

Further, nothing in Hahn would have led one of ordinary skill in the art to conclude that strontium may be capable of combating the inflammatory process *per se* or indeed capable of treating inflammation at the sub-dermal level. Hahn makes no specific mention of the desirability that the compositions should pass into the sub-dermal layers of the skin, which is an essential aspect of the present invention. Applicant also notes that the passing reference to "skin penetration enhancers" at col. 17, line 27 of Hahn, is merely presented in the context of a laundry list of potential components that may be provided in topical formulations. These are generally present to remove natural skin surface associated products (e.g. loose skin flakes, sebaceous gland secretory products) as well as to remove cosmetic products and contaminants from air or other sources so that the active ingredient may achieve better contact with the cells at the skin's surface. Accordingly, Applicant submits that, in light of the disclosure of the document as a whole (which relates solely to surface treatment of the skin), one of ordinary skill in the art

would have not been motivated to use a skin penetration enhancer in order to achieve sub-dermal penetration of the active strontium compounds.

Thus, Hahn is directed towards formulations and methods for reducing skin irritation. Primarily, Hahn is concerned with compositions that inhibit skin irritation resulting from chemical irritants in topical products (e.g., cosmetics) and from environmental conditions (e.g., extremes in temperature and humidity). This reference is therefore concerned with the use of strontium as an anti-irritant for conditions associated with the surface of the skin. Hahn lists typical symptoms of irritation (column 2, lines 2-4) and includes "itching (pruritis), stinging, burning, tingling, "tightness", erythema (redness) or edema (swelling)". The latter two symptoms are non-specific symptoms, which are often, but not exclusively, associated with inflammation. However, Applicant submits that no specific mention is made of inflammation in the reference. Notably, the mere existence of such "symptoms or signs" is not necessarily an indication that an inflammatory reaction has occurred. Nor is it the case that an agent that is capable of treating such symptoms/signs is necessarily capable of combating any underlying inflammatory process that may be responsible for these. Inflammation is a host's "repair" response to "harmful" exposure to chemical agents or physical conditions, and can involve both short and longer term biological reactions. These biological reactions may or may not lead to a number of clinically recognized symptoms, for instance pain. Both local anesthetics (e.g., lidocaine) and non-NSAID analgesic agents (e.g., acetaminophen) will reduce the pain symptom, but neither of these agents will affect the underlying inflammatory reaction. This is just one of many examples showing that it is possible to reduce or eliminate "symptoms" (e.g., pain, irritation, etc.) which may be associated with inflammation without affecting the underlying inflammatory process.

De Lacharriere is concerned with compositions for the treatment and/or alleviation of pain associated with certain skin disorders. It therefore relates to treatment of pain (not inflammation) which only affects the surface of the skin. De Lacharriere does not disclose the use of strontium-containing compositions for the treatment of any sub-dermal conditions, let alone sub-dermal inflammation. Further, the Examiner cites column 1 of De Lacharriere, which speculates on conditions or disorders that involve substance P. Amongst the skin disorders that are specifically mentioned in the reference are psoriasis and acne rosacea (lines 51 and 54). However, these are conditions that affect the surface of the skin (psoriasis, for example, is a skin disease that is well known to produce a number of skin surface symptoms, including dry, itchy, red patches). Also, strictly speaking, the conditions listed in column 1 of De Lacharriere are not those that are proposed to be treated with the metal salts described in the reference. Acne rosacea is, however, mentioned later in the document in the context of the invention (see, e.g., column 2, line 41). In this regard, Applicant submits that the treatment of acne rosacea disclosed in De Lacharriere does not specifically teach the treatment of any associated inflammation. Moreover, Claim 14 does not read onto the treatment of acne vulgaris *per se*, but is directed to the treatment of sub-dermal inflammation which is "associated with" such a condition. A clear distinction exists between treatment of pain associated with a condition, e.g., acne rosacea, and treatment of any underlying inflammatory process.

The Examiner also states that De Lacharriere teaches the use of strontium in treating "inflammatory diseases (such as, for example, rheumatoid arthritis)". However, this statement is made solely in the context of the background discussion to the invention and it does not specifically teach that strontium is effective in treating inflammatory diseases per se as the Examiner appears to suggest. Rather, the teaching of this reference relates to the use of certain

metal salts as substance P antagonists for the treatment of dermal (i.e. topical) pain associated with certain, well-defined skin conditions (see, e.g., column. 1, lines 9-17; column 2, lines 36-41). In this respect, the invention of De Lacharriere is essentially based on the hypothesis that a substance P antagonist will have an analgesic effect.

Furthermore, in contrast to De Lacharriere, the present invention is not concerned with treating skin disorders or pathological processes associated with substance P. It has in fact now been found that strontium does not exert its effects as a substance P antagonist when treating inflammation because substance P is not involved in the pathology of this condition.

Denhem discloses that radiation therapy can induce inflammation in the skin tissues. Remington's teaches that locally applied DMSO, in concentrations above 50%, breaks down collagen, and has anti-inflammatory and local anesthetic effects (page 1121, second column, last paragraph). Accordingly, De Lacharriere, Denhem and Remington do not remedy the deficiencies of Hahn, i.e., use of strontium in combating sub-dermal, soft tissue inflammation.

Applicant also submits that the fact that strontium is effective in combating sub-dermal inflammatory processes (especially when topically applied) is surprising for the following reasons:

In the skin, it is possible to expose the skin surface cells to controlled conditions with very high concentrations of strontium in the absence of potentially antagonistic components (e.g. calcium, see below) for a defined period of time. Similarly, in order to use strontium to affect cells and biological processes below the skin's surface, it could be expected that strontium would have to be able to reach a relatively high concentration (in the absence of antagonistic components) at the sub-dermal location where it is intended to have its effect. However, one of ordinary skill in the art would not expect that such conditions could be achieved. First of all, in

the case of a topically applied medicament, the outer layer of the skin represents a highly effective barrier preventing influx of the medicament. Second, because strontium will be present as positively charged ions in an aqueous solution and most biological constituents have a negative charge, one of ordinary skill in the art would expect that both the outer skin barrier as well as ionic binding would prevent more than homeopathic amounts of strontium from reaching sub-dermal locations, even in the presence of a skin penetration enhancer, such as DMSO. In fact, at sub-dermal sites, high extracellular concentrations of the very similar calcium ion are also present, which is likely to inhibit the action of strontium. Strontium and calcium ions are very similar with respect to both their physical and biological effects, and both have considerable bioactivity. Accordingly, even low local concentrations of calcium are known to have significant adverse effects when administered intradermally or intramuscularly. In this regard, Applicant submits that such adverse effects could similarly be expected for sub-dermally administered strontium. This knowledge teaches away from strontium's sub-dermal use in accordance with the invention.

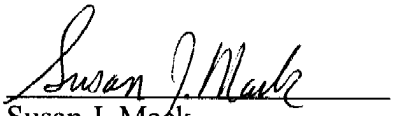
In conclusion, Applicant submits that the person having ordinary skill in the art, based on the teachings of the cited references, either alone or in combination, would not have been motivated to use strontium in combating sub-dermal inflammation in the soft tissues. Further, Applicant submits that because of the similarities of strontium to calcium, the art teaches away form the present invention. Accordingly, Applicant submits that the present invention is not obvious over cited references and thus respectfully requests withdrawal of the rejection under 35 U.S.C. § 103(a).

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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